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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/616,849	07/14/2000	Julja Burchard	9301-044	6450
20583	7590	01/31/2007		
JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			EXAMINER FORMAN, BETTY J	
			ART UNIT	PAPER NUMBER
			1634	

  

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	01/31/2007	PAPER

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/616,849  
Filing Date: July 14, 2000  
Appellant(s): BURCHARD, JULJA

**MAILED**  
**JAN 31 2007**  
**GROUP 1600**

Adriane M. Antler  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 7 November 2006 appealing from the Office action mailed 13 January 2006.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

Art Unit: 1634

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

4,900,659	LO et al	02-1990
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6,344,316	LOCKHART et al	02-2002
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Lockhart et al, "Expression Monitoring by Hybridization to High-Density Oligonucleotide Arrays", Nature Biotechnology, vol. 14 (14 December 1996), pp 1675-1680.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 103***

Claims 27, 29-30, 33-39, 38, 40, 42-54, 59-60, 64-65, 67, 73, 90-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al (U.S. Patent No. 4,900,659, issued 13 February 1990) in view of Lockhart et al (nature Biotechnology, 1996, 14: 1675-1680).

Art Unit: 1634

Regarding Claim 27, Lo et al disclose a method for evaluating a polynucleotide probe comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of molecules comprising the target chromosomal DNA e.g. strain 53414 (Column 8, lines 13-28) and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425) wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1). Furthermore, Lo et al teach the method whereby a binding property (i.e. target specificity) of the probe is evaluated (Column 3, lines 30-39) and wherein the probe is complementary to at least a hybridizable portion of the target (Column 9, line 31-Column 10, line 50).

Lo et al teach the samples comprising predetermined sequences i.e. fragmented chromosomal DNA from *N. gonorrhoeae* and to have preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66) but they do not specifically teach the probes have a predetermined base sequence.

However, Lockhart et al teach a very similar method for evaluating a polynucleotide probe comprising hybridization of probes to targets wherein the base sequence of the probes is predetermined and complementary to at least a part of the target (i.e. from 600 bases of the 3' end of translated region of RNA/specific cytokine RNA) and comparing the hybridization to a second sample comprising a plurality of different polynucleotides i.e. complex RNA population (page 1680, left column). Lockhart et al further teach their method of probe selection, based on sequence information, "provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.....simultaneous monitoring of tens of thousands of genes" (Abstract). It would have been obvious to one of ordinary skill in the art

Art Unit: 1634

at the time the claimed invention was made to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart (Abstract).

Regarding Claim 29, Lo et al disclose the method wherein the target in the first sample is a sequence of a gene from an organism i.e. *N. gonorrhoeae* chromosomal DNA (Column 4, line 44-Column 5, line 65). It is noted that the claim recites "a nucleotide sequence of a gene". The claim does not require the target be a complete gene or transcript but instead merely requires a sequence of a gene. Furthermore, the claim recites, "probe to a target" but does not require the probe comprises a complete target. As such, the hybridization of fragmented chromosomal DNA to chromosomal DNA taught by Lo et al meets the limitations of the claim. Furthermore, Lockhart et al teach the target is from a gene transcript (page 1680, left column).

Regarding Claim 30, Lo et al disclose the method wherein the polynucleotide molecules in the second sample comprise sequences of a plurality of genes of an organism (i.e. chromosomal DNA, Column 8, line 13-Column 9, line 17). And Lockhart et al teach the second sample comprises sequences from genes or gene transcripts (page 1680, left column).

Regarding Claims 33-35, Lo et al disclose the method wherein at least 99% of the polynucleotides in the first sample comprise the target sequence e.g. chromosomal DNA from *N. gonorrhoeae* (Column 8, lines 13-28). And Lockhart et al teach the polynucleotides in the first sample comprise the target sequence i.e. the 3' region of each RNA (page 1680, left column).

Regarding Claim 36, Lo et al disclose the method wherein the second sample does not comprise the target (i.e. chromosomal DNA from *N. gonorrhoeae*) but instead comprises chromosomal DNA from *N. meningitides* (Column 8, lines 13-28). And Lockhart et al teach the molecules of the second sample do not comprise the target i.e. complex RNA, not cytokine RNA (page 1680, left column).

Art Unit: 1634

Regarding Claims 37, 39, 42, 92 and 94 Lo et al disclose a method for evaluating a polynucleotide probe comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of molecules comprising the target chromosomal DNA e.g. strain 53414 (Column 8, lines 13-28) and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425) wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1).

Furthermore, Lo et al teach their method screens closely related samples to analyze probe-specific probes (Column 3, lines 30-39) wherein their method provides for screening nucleotide sequences that are specific for a "genetically distinct group" (Column 4, lines 15-17 and 18-42). Which clearly suggests their method is useful for wild-type and mutants (e.g. deletion mutants). Hence, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of Lo et al to screen genetically distinct groups (e.g. mutants and/or wild-type samples) to thereby screen and analyze mutants and/or wild-type-specific probes as they suggest (Column 3, lines 30-39 and Column 4, lines 15-17).

Regarding Claim 38, Lo et al disclose the method wherein the second sample comprises polynucleotides comprising the target and a plurality of different molecules comprising a different sequence, not the target. Lo et al teach the second sample comprises chromosomal DNA from different *N. meningitidis* strains and from *N. gonorrhoeae* strains (Column 8, lines 13-28). Lo et al teach that the *N. meningitidis* strains do not comprise the target while the *N. gonorrhoeae* strains do comprise the target as evidenced by the *N. gonorrhoeae* detection taught

Art Unit: 1634

by Lo et al (Column 10, line 51-Column 12, line 65). And Lockhart et al teach the similar method wherein the second sample comprises the target and different molecules i.e. "all known genes" from the organism (page 1680, left column).

Regarding Claim 40, Lo et al disclose the method wherein the first sample further comprises molecules that do not comprise the target e.g. chromosomal regions homologous between *N. meningitides* and *N. gonorrhoeae* (Column 3, lines 10-30) and the second sample lacks molecules comprising the target i.e. the second sample comprises organism-specific chromosomal DNA i.e. DNA from *N. meningitides* and not having chromosomal DNA from *N. gonorrhoeae* (i.e. target, Column 8, lines 13-28).

Regarding Claims 43-47, Lo et al disclose the method wherein the first sample further comprises molecules that do not comprise the target e.g. chromosomal regions homologous between *N. meningitides* and *N. gonorrhoeae* (Column 3, lines 10-30) and the second sample comprises polynucleotides comprising the target and a plurality of different polynucleotides comprising different sequences, not the target. In this embodiment the first and second samples each comprises sample spots of *N. meningitides* and sample spots of *N. gonorrhoeae* wherein the first sample spots have 500 nanograms chromosomal DNA and the second sample spots have 5 picograms of chromosomal DNA thereby providing amounts of polynucleotides differing by at least a factor of 100 (Column 11, lines 29-42). The open claim language "comprising" encompasses the first sample having polynucleotide not having the target i.e. *N. meningitides*.

Regarding Claim 48-54, Lo et al teaches the probe evaluation method wherein the amount/abundance of polynucleotide in the first sample is the same as the amount/abundance in the second sample (Column 11, lines 29-42) and therefore differs by no more than a factor of two or by no more than 1% as claimed.

Regarding Claim 59, Lo et al disclose the method wherein the polynucleotides in the first sample are detectably labeled (Column 11, lines 43-65).

Art Unit: 1634

Regarding Claim 60, Lo et al disclose the method wherein the polynucleotides in the first sample are detectably labeled (Column 11, lines 43-65).

Regarding Claim 64, Lo et al disclose the method wherein the polynucleotide probe is attached to the surface of the support i.e. via hybridization to the immobilized chromosomal DNA (Column 8, lines 50-65).

Regarding Claim 65, Lo et al disclose the method wherein the probe is one of a plurality of probes (Column 9, line 14-Column 10, line 50).

Regarding Claim 67, Lo et al disclose a method for evaluating a plurality of polynucleotide probes comprising a predetermined sequence. The method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of molecules comprising the target chromosomal DNA e.g. strain 53414 (Column 8, lines 13-28) and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425) wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1) and wherein the probe is complementary to at least a hybridizable portion of the target (Column 9, line 31-Column 10, line 50).

Lo et al teach the samples comprising predetermined sequences i.e. fragmented chromosomal DNA from *N. gonorrhoeae* and to have preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66) but they do not specifically teach the probes have a predetermined base sequence.

However, Lockhart et al teach a very similar method for evaluating a polynucleotide probe comprising hybridization of probes to targets wherein the base sequence of the probes is predetermined and complementary to at least a part of the target (i.e. from 600 bases of the 3'

Art Unit: 1634

end of translated region of RNA/specific cytokine RNA) and comparing the hybridization to a second sample comprising a plurality of different polynucleotides i.e. complex RNA population (page 1680, left column). Lockhart et al further teach their method of probe selection, based on sequence information, "provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.....simultaneous monitoring of tens of thousands of genes" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart (Abstract).

Regarding Claim 73, Lo et al disclose the method wherein the polynucleotide probes are attached to the surface of the support i.e. via hybridization to the immobilized chromosomal DNA (Column 8, lines 50-65).

Regarding Claim 90, Lo et al disclose the method wherein the polynucleotides molecule comprising the target are the same i.e. chromosomal DNA from *N. gonorrhoeae* (Columns 5-6).

Regarding Claim 91, Lo et al disclose a method for evaluating a plurality of polynucleotide probes comprising a predetermined sequence. The method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of molecules comprising the target chromosomal non-homologous DNA and a plurality of molecules that do not comprise the target i.e. homologous DNA (Column 3, lines 10-30) and the second sample comprises a plurality of different polynucleotides and do not comprise the target (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 (Column 8, lines 9-49) wherein each probe comprises a predetermined sequence Column 5, lines 18-65). Lo et al teach the probes are predetermined nucleotide sequences wherein the probes are predetermined as being

Art Unit: 1634

fragmented chromosomal DNA from *N. gonorrhoeae* and having preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66; Column 10, line 51-Column 12, line 65). Lo et al further teach the hybridization ratio is used as a measure of the binding property (Column 12, lines 10-65 and Claim 1).

Lo et al teach the samples comprising predetermined sequences i.e. fragmented chromosomal DNA from *N. gonorrhoeae* and to have preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66) but they do not specifically teach the probes have a predetermined base sequence.

However, Lockhart et al teach a very similar method for evaluating a polynucleotide probe comprising hybridization of probes to targets wherein the base sequence of the probes is predetermined and complementary to at least a part of the target (i.e. from 600 bases of the 3' end of translated region of RNA/specific cytokine RNA) and comparing the hybridization to a second sample comprising a plurality of different polynucleotides i.e. complex RNA population (page 1680, left column). Lockhart et al further teach their method of probe selection, based on sequence information, "provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.....simultaneous monitoring of tens of thousands of genes" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart (Abstract).

Regarding Claim 93, Lo et al disclose a method for evaluating a plurality of polynucleotide probes comprising a predetermined sequence. The method comprising determining a ratio of the amount of hybridization of polynucleotides in a first sample to the probe and the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of molecules comprising the target chromosomal

Art Unit: 1634

non-homologous DNA and a plurality of molecules that do not comprise the target i.e. homologous DNA (Column 3, lines 10-30) and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 (Column 8, lines 9-49) wherein each probe comprises a predetermined sequence Column 5, lines 18-65). Lo et al teach the probes are predetermined nucleotide sequences wherein the probes are predetermined as being fragmented chromosomal DNA from *N. gonorrhoeae* and having preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66). As such, Lo et al teach the claimed invention (Column 10, line 51-Column 12, line 65). Lo et al further teach the hybridization ratio is used as a measure of the binding property (Column 12, lines 10-65 and Claim 1).

Lo et al teach the samples comprising predetermined sequences i.e. fragmented chromosomal DNA from *N. gonorrhoeae* and to have preferably about 256 base pairs, but more than 12 (Column 5, lines 15-66) but they do not specifically teach the probes have a predetermined base sequence.

However, Lockhart et al teach a very similar method for evaluating a polynucleotide probe comprising hybridization of probes to targets wherein the base sequence of the probes is predetermined and complementary to at least a part of the target (i.e. from 600 bases of the 3' end of translated region of RNA/specific cytokine RNA) and comparing the hybridization to a second sample comprising a plurality of different polynucleotides i.e. complex RNA population (page 1680, left column). Lockhart et al further teach their method of probe selection, based on sequence information, "provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.....simultaneous monitoring of tens of thousands of genes" (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply known sequence analysis for probe selection as taught by Lockhart et al to the probe selection method of Lo et al for the expected

Art Unit: 1634

benefit of obtaining useful probes based on the growing body of sequence information for simultaneous monitoring tens of thousands of genes as taught by Lockhart (Abstract).

Regarding Claims 95-99, Lo et al disclose the method wherein the first sample further comprises molecules that do not comprise the target e.g. chromosomal regions homologous between *N. meningitides* and *N. gonorrhoeae* (Column 3, lines 10-30) and the second sample comprises polynucleotides comprising the target and a plurality of different polynucleotides comprising different sequences, not the target. In this embodiment the first and second samples each comprises sample spots of *N. meningitides* and sample spots of *N. gonorrhoeae* wherein the first sample spots have 500 nanograms chromosomal DNA and the second sample spots have 5 picograms of chromosomal DNA thereby providing amounts of polynucleotides differing by at least a factor of 100 (Column 11, lines 29-42). The open claim language "comprising" encompasses the first sample having polynucleotide not having the target i.e. *N. meningitides*.

Regarding Claims 100-104, Lo et al teaches the probe evaluation method wherein the amount/abundance of polynucleotide in the first sample is the same as the amount/abundance in the second sample (Column 11, lines 29-42) and therefore differs by no more than a factor of two or by no more than 1% as claimed

Claims 61-63, 66, 74-75, 84-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al (U.S. Patent No. 4,900,659, issued 13 February 1990) in view of Lockhart et al (Nature Biotechnology, 1996, 14: 1675-1680) as applied to Claims 27 and 67 above and further in view of Lockhart "Lockhart Patent" (U.S. Patent No. 6,344,316 B1, filed 25 June 1997).

Regarding Claims 61-63, 66, 74-75, 84-85, Lo et al and Lockhart et al teach the methods of probe analysis as detailed above wherein the polynucleotide probes are detectably

Art Unit: 1634

labeled (Lo, Column 11, lines 43-65) but they do not teach the polynucleotides are differentially labeled with fluorescent labels and they do not teach the probes are in an array of probes wherein different probes are attached to different locations on the array.

However, the Lockhart Patent teaches a similar method for evaluating a binding property of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising: comparing the amount of hybridization of polynucleotide in a first sample to the probe with the amount of hybridization of polynucleotides in a second sample to the probe wherein the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence and said second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide comprises a sequence that is different from the sequences of other polynucleotides and wherein at least 75% of the polynucleotides in the first sample are polynucleotides comprising said target sequence thereby evaluating said binding property of said probe wherein each different polynucleotide in the second sample does not comprise the target sequence wherein the target sequence is a gene sequence and wherein the probes comprise perfect match and mismatch probes (Column 36, lines 24-47 and Example 1, Column 70, line 58-Column 73, line 46) wherein different probes are attached to different locations on the array wherein cross-hybridization is minimized (Column 37, line 44-56) and whereby a high-density array of probes are optimized (Column 36, lines 25-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the probe array of the Lockhart Patent to the probe analysis of Lo et al for the obvious benefits of optimizing a high-density array of probes as desired by the Lockhart Patent (Column 36, lines 25-27).

The Lockhart Patent further teaches fluorescent labeling wherein different samples are differentially labeled (Column 24, lines 54-67). The Lockhart Patent further provides motivation for using their fluorescent labeling as cited below:

Art Unit: 1634

A fluorescent label is preferred because it provides a very strong signal with low background. It is also optically detectable at high resolution and sensitivity through a quick scanning procedure. The nucleic acid samples can all be labeled with a single label, e.g., a single fluorescent label. Alternatively, in another embodiment, different nucleic acid samples can be simultaneously hybridized where each nucleic acid sample has a different label. For instance, one target could have a green fluorescent label and a second target could have a red fluorescent label. The scanning step will distinguish sites of binding of the red label from those binding the green fluorescent label. Each nucleic acid sample (target nucleic acid) can be analyzed independently from one another.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to fluorescently label the different polynucleotides of Lo et al for the expected benefits of providing a very strong signal with low background which is also optically detectable at high resolution and sensitivity through a quick scanning procedure as taught by the Lockhart Patent (Column 24, lines 54-57). It would have been further obvious to differentially label the different polynucleotides of Lo et al to thereby provide for independent analysis of simultaneously hybridized polynucleotides as taught by the Lockhart Patent (Column 24, lines 59-67).

#### **(10) Response to Argument**

B1: Appellant asserts that the combination of the references does not render the claimed invention obvious and one skilled in the art would not have been motivated to combine the teachings so as to render the invention obvious.

Appellant provides an analysis of Lo and states that Lo does not teach or suggest determining the sequence of the probes. Appellant acknowledges that Lo selects probes based on a hybridization ratio, but asserts that because Lo used randomly generated fragments of chromosomal DNA in the probe selection, the base sequences of the probes were not known. Appellant asserts that because Lo does not teach a predetermined base sequence, one of skill in the art would not be motivated to use sequence information in the method of Lo.

Appellant's assertion is noted, but is not persuasive to overcome the rejection for at least two reasons. First, as cited above, Lockhart provide clear motivation for evaluating

Art Unit: 1634

probes using probes having predetermined base sequence i.e. the method of probe selection, based on sequence information, “provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.....simultaneous monitoring of tens of thousands of genes” (Abstract). Second, Appellant’s assertion that one would not be motivated to alter the method of Lo because Lo uses randomly generated fragments, does not alter the fact that Lockhart provides the clear motivation as provided.

Appellant provides an analysis of the Lockhart reference and asserts that Lockhart teaches selection of probes based on difference of binding properties of perfect match (PM) and mismatch (MM) probes, but not according to a ratio between the amount of a probe’s hybridization to the pool of specific cytokine RNA and the amount of probe’s hybridization to the complex RNA population not containing the specific cytokine RNA.

Appellant’s interpretation of Lockhart is noted. The examiner agrees that Lockhart is interested in expression monitoring and does use arrays of PM and MM probes in the expression analysis. However, the passages cited in the Office Action and relied upon to reject the instantly claimed methods are the passages of Lockhart that teach selection of probes for the arrays used in expression analysis, that selection based on a comparison of hybridization between probes of known sequence (Abstract and page 1680, left column, second full paragraph). Lockhart specifically teaches “probes selection rules” and provides details including starting with probes of known sequence (page 1680, left column, second full paragraph, lines 1-7).

Appellant asserts that Lo does not teach a first or second sample comprising a target sequence as instantly claimed. Appellant asserts that because “comprising” is construed as “containing at least” an entire target sequence is required by the instant claims. Appellant further asserts that the fragmented chromosomal DNA of Lo would be comprise an entire target sequence as required by the claims. The assertions are noted. However, the instant claims do not define or require a specific target length or sequence so as to define the claimed target over

Art Unit: 1634

any sequence (e.g. 2 nucleotides) in the art. The claim merely requires a target sequence and a probe that is hybridizable to a portion of the target. Lo specifically teaches probes that hybridize to the genomic fragments (e.g. Column 17, lines 10-45). Any nucleic acid sequence within the genomic fragments that hybridize to the probes is encompassed by the broadly claimed "target sequence" and probes that are hybridizable thereto. Hence, Lo teaches the target as broadly claimed and merely lacks a teaching of probes having a predetermined sequence.

Appellant asserts that Lo does not teach the samples as claimed. The assertion is noted however, as cited above, Lo teaches the samples wherein the first sample comprises a plurality of molecules comprising the target chromosomal DNA e.g. strain 53414 (Column 8, lines 13-28) and the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421, 53422, 53423, 53424, 53425) wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1).

Appellant asserts that the examiner has used hindsight reasoning to reconstruct the claimed invention. In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Furthermore, as stated in the body of the rejection and reiterated above, Lockhart provides clear motivation for using probes of predetermined base sequence.

Art Unit: 1634

Appellant asserts that the motivation provided by the Office "is not adequate as evidence of motivation and suggestion" because the Office does not provide evidence regarding how the sequence information may benefit Lo's method, or evidence as to which sequences are useful. For these reasons, Appellant asserts that the motivation provided by the Office is "nothing more than '[b]road conclusory statements regarding the teaching of multiple references' which, standing alone, 'are not 'evidence.'" Appellant's assertion is noted but is not found persuasive. As stated above, Lockhart clearly provides motivation for using probes of known sequence (see Abstract).

Appellant asserts that the Office incorrectly characterizes the teaching of Lo because the reference teaches does not teach that each dot comprises a mixture of chromosomal DNA from two or more different strains. Appellant appears to be asserting that the claimed "plurality of different polynucleotide molecules" is defined as molecules from different sources. The assertion is noted. However, the claims are not so limited. In contrast, the claims merely require different molecules. The sheared DNA (as cited by Appellant, column 22, lines 11-15) provides multiple fragments. Furthermore, Lo (column 17, lines 20-24) teaches their method of probe selection comprises:

- a. forming a separate test dot on a matrix for each sample that said nucleotide sequence is to be screened against wherein each test dot comprises purified DNA in single stranded form from one of said samples;

B2: Appellant asserts that Lo et al do not teach the first sample wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence. As stated above, Lo et al teach the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1). Because the target sequence is broadly defined as having a hybridizable sequence and because Lo et al teach hybridizable chromosomal DNA in each spot, Lo et al teach the target sequence-containing molecules as broadly claimed.

Art Unit: 1634

B3: Appellant asserts that Lo does not motivate or suggest target sequences or gene sequences are required in Claim 29. The assertion is noted, however claim 29 is not so limited. The claim merely defines the target as “a nucleotide sequence from a gene, gene transcript of a cell or organism, or of an mRNA, cDNA or cRNA derived therefrom.” Hence, the claim defines any nucleotide sequence (e.g. 2 nucleotides) from a gene sequence. Furthermore, the claims do not require that the target nucleotide sequence be a known sequence of nucleotides. The claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target. Hence, Appellants arguments regarding known target sequence are not commensurate in scope with the claims.

B4: Appellant asserts that Lo does not teach the second sample comprise a deletion mutant or organisms that does not express the gene. The assertion is note but not found persuasive because as stated above, Lo et al teach their method screens closely related samples to analyze probe-specific probes (Column 3, lines 30-39) wherein their method provides for screening nucleotide sequences that are specific for a “genetically distinct group” (Column 4, lines 15-17 and 18-42). Which clearly suggests their method is useful for wild-type and mutants (e.g. deletion mutants). Hence, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of Lo et al to screen genetically distinct groups (e.g. mutants and/or wild-type samples) to thereby screen and analyze mutants and/or wild-type-specific probes as they suggest (Column 3, lines 30-39 and Column 4, lines 15-17).

B5: Appellant asserts that Lo et al do not teach a second sample does not comprise the target molecule. The argument has been considered but is not found persuasive because as stated above, both references teach the second sample does not contain the broadly claimed target i.e. Lo et al teach the second sample does not comprise the target (i.e. chromosomal DNA from *N. gonorrhoeae*) but instead comprises chromosomal DNA from *N. meningitides* (Column 8,

Art Unit: 1634

lines 13-28) and Lockhart et al teach the molecules of the second sample do not comprise the target i.e. complex RNA, not cytokine RNA (page 1680, left column).

B6: Appellant asserts that the references do not teach the plurality of different nucleotide molecules in the second sample and claimed. The assertion is noted, however as stated above, Lo et al teach the second sample comprises chromosomal DNA from different *N. meningitides* strains and from *N. gonorrhoeae* strains (Column 8, lines 13-28). Lo et al teach that the *N. meningitides* strains do not comprise the target while the *N. gonorrhoeae* strains do comprise the target as evidenced by the *N. gonorrhoeae* detection taught by Lo et al (Column 10, line 51-Column 12, line 65) and Lockhart et al teach the similar method wherein the second sample comprises the claimed different molecules i.e. "all known genes" from the organism (page 1680, left column). Furthermore, Lockhart specifically teaches the second sample is used to determine which probes "were poor or promiscuous hybridizers", (page 1680, left column second full paragraph, lines 14-20) thereby providing the motivation for using the second sample as claimed.

B7: Appellant asserts that the references do not teach the sample ratios as claimed because they teach randomly generated fragments and therefore do not teach the amount of any known target sequence. The assertion is noted, however as stated above, the claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target. Hence, Appellants arguments regarding known target sequence are not commensurate in scope with the claims. Furthermore, Lo et al teach the method wherein the first sample further comprises molecules that do not comprise the target e.g. chromosomal regions homologous between *N. meningitides* and *N. gonorrhoeae* (Column 3, lines 10-30) and the second sample comprises polynucleotides comprising the target and a plurality of different polynucleotides comprising different sequences, not the target. In this embodiment the first and second samples each comprises sample spots of *N. meningitides* and sample spots of *N. gonorrhoeae* wherein the first sample spots have 500 nanograms chromosomal DNA and the

Art Unit: 1634

second sample spots have 5 picograms of chromosomal DNA thereby providing amounts of polynucleotides differing by at least a factor of 100 (Column 11, lines 29-42). The open claim language "comprising" encompasses the first sample having polynucleotide not having the target i.e. *N. meningitides*. Lo et al also teaches the probe evaluation method wherein the amount/abundance of polynucleotide in the first sample is the same as the amount/abundance in the second sample (Column 11, lines 29-42) and therefore differs by no more than a factor of two or by no more than 1% as claimed.

C1: Regarding the rejections over Lo in view of the Lockhart reference and the Lockhart Patent, Appellant asserts that the Lockhart Patent does not teach the claimed method. The Lockhart Patent is cited for teaching the fluorescent labels and arrays of Claims 61-63, 66, 74-75 and 84-85. Appellant asserts that "one skilled in the art would understand that there is not need to label the polynucleotides in Lo's sample, much less to label them differentially. In addition, a person skilled in the art would also understand that, in such a method, hybridization of a probe to different samples can be detected without the need of differential labeling, because the different samples, i.e., different test dots, are spatially addressable. Thus, a person skilled in the art would not be motivated to differentially label with fluorescent labels the polynucleotides of Lo." Appellant's comments are noted, however the comments assert opinions of "one skilled in the art". However, the asserted opinions appear to be unsupported by any evidence of such opinions. Therefore, the assertions are deemed opinion of counsel and not of one skilled in the art. Furthermore, as stated above the rejection, the differential labeling and array of the Lockhart Patent permit high-density array hybridization and differential detection very strong signal with low background as desired in the art (Column 24, lines 54-67; Column 36, lines 25-27; Column 37, lines 44-56).

C2: Appellant asserts that because Lo does not know the base sequence of the probe, Lo cannot suggest the sample of Claim 75. The assertion is noted, however, the Lockhart Patent clearly teaches the advantages of hybridization wherein the sample comprises multiple different

Art Unit: 1634

polynucleotides whereby differentially labeled nucleotides can be analyzed independently. Therefore, it would have been further obvious to differentially label the different polynucleotides of Lo et al to thereby provide for independent analysis of simultaneously hybridized polynucleotides as taught by the Lockhart Patent (Column 24, lines 59-67).

C3: Appellant asserts that because the *N. gonorrhoeae* and *N. meningitides* have high sequence homology, one skilled in the art would expect that Lo's second sample might contain polynucleotides also in the first sample. The assertion is noted but is not found persuasive because Claim 85 merely requires that the second sample lack polynucleotides of the first sample. Appellant appears to be asserting that no polynucleotide sequences in the first sample are presence in the second. However, the claims are not so limited. The claims merely require that the second sample lack some (undefined) polynucleotides of the first sample. Hence, any nucleotide sequence (e.g. any two bases) in the first sample, not presence in the second sample. Because the first and second polynucleotide samples are different, as acknowledged by Appellant, the second sample lacks some polynucleotides as claimed.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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**PRIMARY EXAMINER**

  
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